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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/582,492 | 03/06/2002 | Elizabeth S. Light | 142/003/PCT | 8768 |

23874 7590 04/05/2005

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| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/582,492 | LIGHT ET AL. | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *1/18/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,7,17,19 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,17,19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendments filed 1/18/05 have been entered. Claims 1, 3, 7, 17, 19, and 22 are pending. Claims 1, 3, and 7 have been amended. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. THIS ACTION IS FINAL.

### *Claim Rejections - 35 USC § 102*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Meijer *et al.* (WO 95/22626).

Meijer *et al.* teach a reagent for detecting human papillomavirus DNA comprising a plurality of DNA probes capable of specifically hybridizing to high-risk HPV DNA but not low-risk HPV DNA. In particular, Meijer *et al.* teach a mixture of probes specific for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56, and 58, and that this mixture does not contain probes specific for a variety of "low risk" HPV types (p. 16, lines 15-23).

Thus, the reagent taught by Meijer et al. is considered to include a first genomic HPV DNA probe set that comprises a plurality of nucleic acid fragments of essentially the full-length genomic sequence of each of the HPV types represented in the cocktail. For example, regarding

HPV type 16, the oligonucleotide probes within the "cocktail" taught by Meijer et al. specific for HPV type 16 would be a plurality of fragments, since there would inherently be more than one copy of each probe in the solution, and these are fragments of the full length genomic sequence, as recited by the claim. The same is true for each of types (a)-(f) recited in claim 1.

With regard to claim 17, the probe cocktail taught by Meijer et al. and exemplified on page 30 of Meijer et al. would have inherently been within a container.

***Claim Rejections - 35 USC § 103***

4. Claims 3 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer *et al.* in view of Orth *et al.* (US 5981173).

Meijer *et al.* teach a reagent for detecting human papillomavirus DNA comprising a plurality of DNA probes capable of specifically hybridizing to high-risk HPV DNA but not low-risk HPV DNA. In particular, Meijer *et al.* teach a mixture of probes specific for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56, and 58, and that this mixture does not contain probes specific for a variety of "low risk" HPV types (p. 16, lines 15-23).

Thus, the reagent taught by Meijer et al. is considered to include a first genomic HPV DNA probe set that comprises a plurality of nucleic acid fragments of essentially the full-length genomic sequence of each of the HPV types represented in the cocktail. For example, regarding HPV type 16, the oligonucleotide probes within the "cocktail" taught by Meijer et al. specific for HPV type 16 would be a plurality of fragments, since there would inherently be more than one copy of each probe in the solution, and these are fragments of the full length genomic sequence, as recited by the claim. The same is true for each of types (a)-(f) recited in claim 1, from which

claim 3 depends. Meijer *et al.* further teach that it is advisable to add HPV 59 to the high risk reagent and suggest that the probe cocktail needs to be supplemented when new identified high risk HPVs are found (p. 16, line 26-p. 17, line 5).

With regard to claim 18, the probe cocktail taught by Meijer et al. and exemplified on page 30 of Meijer et al. would have inherently been within a container.

Meijer *et al.* do not teach a reagent that hybridizes to HPV types 68 and 70.

Orth *et al.* teach the genomes of HPV68 and HPV70 and teach that they were cloned from cervical interepithelial neoplasia (ABSTRACT, and throughout). Orth *et al.* teach oligonucleotide probes for the detection of HPV types 68 and 70 (Col. 3, lines 34-44) and teach that these probes can be used in combination with probes derived from other HPV (Col. 3, lines 54-56).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included probes specific for HPV 68 and HPV 70 in the reagents taught by Meijer *et al.* The ordinary practitioner would have been motivated to include the probes to the additionally HPV types in order to follow the explicit guidance provided by Meijer *et al.* to include additional HPV probes for a more complete set of probes for detection of HPV that lead to high risk for the development of cancer.

5. Claims 7 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer *et al.* in view of Bauer *et al.* (US 5639871).

Thus, the reagent taught by Meijer et al. is considered to include a first genomic HPV DNA probe set that comprises a plurality of nucleic acid fragments of essentially the full-length genomic sequence of each of the HPV types represented in the cocktail. For example, regarding

HPV type 16, the oligonucleotide probes within the "cocktail" taught by Meijer et al. specific for HPV type 16 would be a plurality of fragments, since there would inherently be more than one copy of each probe in the solution, and these are fragments of the full length genomic sequence, as recited by the claim. The same is true for each of types (a)-(f) recited in claim 1, from which claim 3 depends. Meijer *et al.* further teach that it is advisable to add HPV 59 to the high risk reagent and suggest that the probe cocktail needs to be supplemented when new identified high risk HPVs are found (p. 16, line 26-p. 17, line 5).

With regard to claim 22, the probe cocktail taught by Meijer et al. and exemplified on page 30 of Meijer et al. would have inherently been within a container.

Meijer *et al.* do not teach a reagent having probes in the concentrations given in claim 7. However, the optimization of hybridization assays by determining ideal probe concentrations was routine in the prior art at the time the invention was made, as is exemplified by Bauer *et al.* who teach "The optimal ration and concentration of probe fragments to be used in the hybridization are determined empirically (Col. 51, lines 60-63)."

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have experimented with different probe concentrations so as to arrive at an optimal concentration for the detection of HPV in a sample. It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in

> degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52 ; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586 . Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372 ; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204 . However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433 ; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308 ; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314 . More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412 ; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213 ; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

For these reasons, the claimed invention is *prima facie* obvious.

6. Claims 1, 3, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (1995) in view of Cox et al. (Am. J. of Obstet. Gynecol., 1995, Vol. 172, p. 946-954).

Nuovo *et al.* teach a reagent for detecting human papillomavirus DNA in a cell sample comprising a plurality of genomic DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments of essentially the full-length genomic sequence of HPV type 16 that detectably hybridize to substantially all of the full length genomic sequence of HPV types 16 and 18, as well as 31, 33, and 35. Nuovo *et al.* teach probe mixes provided by Digene that are made using the entire genome and that contain probes for these groups of HPV subtypes (p. 106, "Probe selection.").

With regard to claim 3, the cross-hybridization of the probes taught by Nuovo *et al.* to the genomic sequences of HPV types 39, 45, 52, 56, 58, 59, 68, and 70 is an necessary property of

the probes taught by Nuovo *et al.* Some cross-hybridization of the full length probe cocktail taught by Nuovo *et al.* to these sequences could be expected under some stringency conditions. Notably, this is evidenced by the instant specification which teaches that full length nick translated genomic probe to HPV 18 hybridizes to 18, 39, 45, 56, 59, 68, and 70 and full length nick translated genomic probe to HPV 33 hybridizes to 16, 31, 33, 35, 45, 52, and 58.

With regard to claims 17 and 19, Nuovo *et al.* teach that they obtain these probes in kits from Digene Diagnostics, and these kits would inherently comprise containers containing the probes.

Nuovo et al. do not teach a reagent that comprises genomic probe sets that are fragments of essentially the full-length genomic sequence of all of the HPV types listed in claim 1.

Cox et al. teach a single reagent that comprises RNA probes to a group of high risk HPV types which includes types 16, 18, 31, 33, 35, 51, 45, 52, and 56 (p. 948). Cox et al. also teach separate assays to test for high risk HPV types 39 and 58 (p. 948), and suggest that the assay they used be expanded to include types 39 and 58 (p. 953, 2$^{nd}$ column).

It would have been prima facie obvious at the time the invention was made to have modified the reagents taught by Nuovo et al. so as to have included additional probes that are made using the entire genome into the mixes taught by Nuovo et al. following the example of Cox et al. who provide a cocktail mix of probes to a host of different high risk HPV sequences. One would have been motivated to provide such a mix in order to have provided a DNA probe cocktail that had the ability to detect many different known high risk HPV types in an assay similar to that used by Cox et al. One would have been motivated to use DNA probes as opposed to RNA probes as taught by Cox et al. because DNA probes are more stable in solution

than RNA probes which are more quickly degraded. With regard to the requirement that these probes "not detectably hybridize to the genomic sequence of a low-risk HPV type" this is considered to be a necessary property of the probe set taught by Nuovo et al. in view of Cox et al. since at very high stringency conditions such cross-hybridization would not be expected. Thus, in view of a secondary consideration, such as an unexpected result, the claimed invention is prima facie obvious.

**Response to Remarks**

The rejection of claims 1, 3, 17, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Troncone et al. (J. Clin. Pathol. 1992, Vol. 45:308-313), as evidenced by Herrington et al. (J. Clin. Pathol. 1989 42:592-600) is WITHDRAWN in view of applicant's amendments to the claims. Likewise, the 102(b) rejection in view of Nuovo et al. is WITHDRAWN.

The rejection of claims 1, 3, 7, 17, 19, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because they contain NEW MATTER is WITHDRAWN in view of the amendments to the claims.

The rejection of claims 3, 7, 19, and 22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is WITHDRAWN in view of the amendments to the claims.

Applicant's remarks all address the withdrawn grounds of rejection and are MOOT since these rejections have all been overcome by the amendments to the claims.. New art rejections are set forth in this office action to address the amendments to the claims.

***Conclusion***

7. Claim 7 is no longer free of the prior art because the amendment to claim 1 is sufficiently broad so as to encompass a reagent comprised of oligonucleotide probes provided these are fragments of the full-length genomic sequence of HPV types as listed in the claims. If the claims were amended to require, for example, probe sets that are made by nick translation of the full length HPV types, the claim 7 would then be free of the prior art because the prior art does not teach a reagent that has all of the recited genomic HPV DNA probes in the recited percentages and the specification teaches an unexpected result wherein the HPV DNA probe sets for the subtypes recited in claim 7 are present in the percentages recited as percentage of TOTAL PROBE in the hybridization mixture. The unexpected result is the specificity with which this probe set is able to detect itself but also HPV of types 39, 45, 52, 56, 58, 59, 68, and 70. Claims which encompass oligonucleotide probes, or probes in any concentration are not commensurate in scope with this unexpected result.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

March 31, 2005